REMARKS

Claims 21-27 and 29-38 are rejected as obvious under 35 U.S.C. § 103(a) over Petre *et al.* (WO 93/24148) in view of Arminjon AU 708777. For the reasons detailed in their previously-filed appeal brief as well as the additional arguments and evidence submitted herewith, the applicants respectfully traverse.

The cited art, alone and in combination, fails to teach or suggest each and every limitation of the claims on appeal, and it fails to provide the ordinary artisan with a reasonable expectation of success.

The cited art fails to teach or suggest a vaccine composition, together with an aluminum salt adjuvant, made by combining the valencies of the present claims, *i.e.*,

1) pertussis toxoid
2) filamentous haemagluttinin,
3) tetanus toxoid,
4) diphtheria toxoid,
5) inactivated poliovirus, and
6) a conjugate of a carrier molecule and a capsular polysaccharide of Haemophilus influenzae type b,

according to the method recited in claim 21.

The Office has failed to clearly and with particularity identify the teachings or suggestions in the prior art to make the presently claimed methods and compositions comprising each of the recited antigens as required. *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed"). A general motivation is legally insufficient. *In re Deuel*, 34 U.S.P.Q.2d 1210, 1216 (Fed. Cir. 1995) ("A general incentive does not make obvious a particular result..."); *In re Obukowicz*, 27 U.S.P.Q.2d, 1063, 1065 (Bd. Pat. App. Int. 1992) (Prior art "that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it . . . does not make the invention obvious."). The applicants respectfully submit

that the cited art does not teach or suggest the particular methods and compositions comprising the particular antigens now being claimed.

The combination of Arminjon *et al.* and Petre *et al.* does not suggest adsorbing tetanus toxoid and diphtheria toxoid onto an aluminum salt before being mixed with the other components or preparing the Hib conjugate in a phosphate buffer before mixing with the other components. The Examiner points to various teachings of Petre *et al.* for the proposition that Petre *et al.* teaches pre-adsorption of tetanus and diphtheria toxoids to aluminum salt before mixing with other components. But a careful reading of Petre *et al.* reveals that its teachings in this regard are limited to HBsAg-containing vaccines. Furthermore, Petre *et al.* teaches that in the formulation of a multivalent vaccine including a Hepatitis B surface antigen (HBsAg), ***all*** the components of the vaccine composition are to be adsorbed onto a suitable adjuvant:

1. Avoiding the use of AH [aluminum hydroxide] to adsorb the HBsAg component in the vaccine formulation [of the invention] also gives rise to a product of markedly superior stability.

   ...

   Preferably the HBsAg is adsorbed on AP [aluminum phosphate]. In particular we have found in human clinical studies that when **AP-adsorbed HBsAg is combined with one or more AH-adsorbed or AP-adsorbed antigens** in a combined vaccine no substantial decrease in immunogenicity occurs.

   P. 2, ll. 31-34.

2. In a further aspect, the invention provides a combined vaccine comprising Hepatitis B surface antigen (HBsAg) adsorbed to AP and an antigen adsorbed to AP or to AH selected from an antigen providing immunity against one or more of the following viruses...

   P. 3, ll. 8-11.

3. In general, the combined vaccine compositions according to any aspect of the invention can be prepared as follows. The required DT, DTPw, DTPa, HA or other components are adsorbed onto a suitable adjuvant, especially AH or AP; HBsAg is adsorbed onto a suitable stabilizing adjuvant, selected as hereinabove described, especially an aluminum salt other than AH. Preferably it is adsorbed onto AP. After allowing time for complete and stable adsorption of the respective components, the different components are combined under appropriate conditions.

   p. 8, l. 35, through p. 9, l. 3.

4. Every Example in Petre *et al.* teaches embodiments in which **all** the antigens are adsorbed onto an aluminum salt.

Neither Petre *et al.* nor Arminjon *et al.* (alone or in combination), suggest preferentially adsorbing diphtheria and tetanus toxins to an aluminum salt before being mixed with antigens other than HBsAg, such as pertussis toxoid, filamentous hemagglutinin, inactivated polio virus, and a Hib capsular polysaccharide-protein conjugate as recited in the present claims.

The fact that Petre *et al.* teaches adsorption of **all** antigens to an adjuvant is particularly relevant to claim 23, which expressly teaches that the IPV valence is added to the other components ***without first being adsorbed onto an aluminum salt***. Petre *et al.*'s teaching is away from such an embodiment.

In addressing claim 23 in the Examiner's Answer on appeal, the Examiner pointed to claim 27 of Petre *et al.* for support for his position that Petre *et al.* teaches instances where only one of the components in the multivalent vaccine is adsorbed to an aluminum salt and the others are not. The applicants respectfully disagree. First, claim 27 merely teaches a composition comprising HBsAg adsorbed to aluminum phosphate and has greater stability than the corresponding vaccine in which HBsAg is adsorbed to aluminum hydroxide. That is, claim 27 is drawn to the inventive feature taught in the specification, which is avoidance of aluminum hydroxide as an adjuvant for HBsAg and the use of other HBsAg adjuvants, such as aluminum phosphate (as indicated in numbered item 1, above). Claim 27's teachings are directed only to the nature of the HBsAg antigen in the claimed composition. It neither teaches nor suggests that the other antigens in a multivalent HBsAg vaccine are not adsorbed onto an adjuvant.

Nor, for the very same reasons just discussed, do claims 6 and 7 (also cited by the Examiner in the Examiner's Answer) teach or suggest that the antigens other than HBsAg need not be adsorbed onto an adjuvant. Claims 6 and 7 both ultimately depend from claim 1, which recites, in part, "A combined vaccine composition comprising Hepatitis B surface antigen (HBsAg) and a number (n) of other antigens **in combination with an adjuvant comprising one or more aluminum salts**..." (emphasis added). Claim 6 merely further limits claim 1 by requiring that the composition comprises an antigen adsorbed to AH selected from diphtheria, tetanus, pertussis, inactivated Polio, Haemophilus influenzae b, and Hepatitis A. And claim 7 recites a composition comprising HBsAg and at least two antigens. There are no teachings in claims 6 and 7 regarding adsorption onto an aluminum adjuvant that differ from the teachings in the remainder of the publication (which are that **all** antigens are adsorbed onto an aluminum salt).

The significance of claim 6 is that it limits the claimed composition to those having an antigen other than HBsAg adsorbed to "AH [aluminum hydroxide]". That is, the purpose of the claim is to limit the **type** of aluminum salt to which one of the antigens is adsorbed, the presumption being that all antigens are adsorbed onto an aluminum salt. Claim 6 does not recite that the antigen is adsorbed to "an adjuvant," which indeed would have suggested that other antigens need not be adsorbed onto an adjuvant.

Nor does the combination of Arminjon *et al.* and Petre *et al.* suggest preparing the Hib conjugate in a phosphate buffer before mixing with the other components of the claimed vaccine. The Examiner has alleged that Arminjon *et al.* teaches that PRP-T should be prepared in a buffer solution before mixing and referred to Arminjon *et al.* p. 6, ll. 33-40. But a careful reading of this passage reveals that it is merely concerned with preparing PRP-T adsorbed to a modified aluminum complex, wherein the aluminum complex is modified by the addition of anions. In particular, it is concerned with whether such anions should be added to the aluminum complex before or after PRP-T. Petre *et al.* does not address the issue of whether PRP-T should be added to a phosphate buffer solution before the addition of other antigens in a multivalent vaccine (as presently claimed). Arminjon *et al.* contains no teachings or suggestion vis-à-vis the order mixing PRP-T with the other antigens recited in the present claims.

Furthermore, the ordinary artisan would not have a reasonable expectation of successfully combining all of the antigens of the present claims to arrive at a composition having efficacy for each of its constituents. As described on page 7 of the specification, results obtained with combination vaccines comprising antigens of pertussis, diphtheria, tetanus, and Hib (PRP or PRP-T) have been mixed, with some reporting decreases in immune response for combinations of antigens. The compositions in the cited art closest to those being claimed appear to be in Examples 12 and 13 of Arminjon *et al.* But Arminjon *et al.* does not describe how the compositions were made and with regard to immunogenicity, states only that the immunogenicity of PRP-T was "satisfactory" in mice. No antibody titer data were provided, nor were any data regarding the antibody titers of the other components given. Petre *et al.* fails to compensate for this deficiency. Thus, the combination of Arminjon *et al.* and Petre *et al.* do not provide the reasonable expectation of success necessary to establish a *prima facie* case of obviousness.

The uncertainty the ordinary artisan faces when combining antigens in a DTaP-Hib vaccine as presently claimed has been acknowledged in the art. Eskola, *J. Infectious Diseases* **174**, S302-5

(1996) (Exhibit A) ("Eskola I"), entitled, "Analysis of *Haemophilus* influenzae Type B Conjugate and Diphtheria-Tetanus-Pertussis Combination Vaccines," states in the introduction:

> Combined vaccines cannot, however, be made by simply mixing vaccines in the same syringe. One must take into consideration all constituents, including stabilizers, preservatives, and adjuvants, and their relative properties and potential chemical and biologic interactions.

p. S302, col. 1 (emphasis added). And in the section entitled, "Implications for the Future," (pp. S304-S305), Eskola states:

> In the next few years, data from vaccine trials will affect the development of combined vaccines. Evidence of the protective efficacy and clinical usefulness of Pa [acellular pertussis] vaccines will be available soon. National vaccination programs will probably start using DTPa instead of DTPw [whole cell pertussis], and new combined vaccines, such as DTPa-Hib and DTPa-IPV-Hib, may become available.
>
> From experience with DTPw-Hib combinations, one could expect interference between Hib, diphtheria, tetanus, and pertussis antigens in the new DTPa-Hib combined vaccines. The clinical significance of this interference must be considered carefully.

(Emphasis added.)

This view was reiterated in Eskola *et al.*, *The Lancet* **348**, 1688 (1996) (Exhibit B) ("Eskola II"), which reported results from administration to subjects of DTaP with Hib conjugate and IPV (through separate injections and combined). Eskola II compared the administration of three vaccines:

1. **DTaP** (pertussis toxoid, filamentous haemagglutinin, pertactin, diphtheria toxoid, tetanus toxoid, aluminium hydroxide))
2. **Hib** (Hib capsular polysaccharide/tetanus toxoid conjugate)
3. **IPV** (inactivated polioviruses type 1, 2, and 3)

alone, or in combinations to four groups. Eskola II reported that the mixture of DTaP, IPV, and Hib interferes with the primary antibody response to poliovirus antigens and, to a much greater extent, Hib, characterizing the immunogenic response to Hib as "poor." *Id.* at 1690. Eskola II noted that three other studies reported significantly lower concentrations of antibodies to Hib in groups receiving mixed DTaP Hib conjugate vaccines compared to groups to which the various vaccines were administered separately. Eskola stated that "[t]he mechanism by which mixing of the vaccines reduced the antibody response is not clear." *Id.* at 1691.

In a similar study, Bell *et al.*, *Vaccine* **16**, 637 (1998) (Exhibit C) administered a combination vaccine of DPT-a (diphtheria, tetanus, acellular pertussis (pertussis toxin + filamentous haemagglutinin))

absorbed with aluminum hydroxide and mixed with PRP-T. It reported a decrease in Hib antibody titers compared to when the PRP-T is administered separately. Bell *et al.* characterized the decrease in Hib immunogenicity as "of potential concern," although Bell *et al.* made no conclusions one way or the other regarding whether the decrease correlated with clinical efficacy. Like Eskola II, Bell *et al.* stated that the explanation for the reduction was unknown, citing five studies reporting similar results.

The inability of one of ordinary skill in the art to determine *a priori* (with a reasonable degree of certainty) the likely efficacy of a particular combination vaccine is further highlighted by comparing observed Hib antibody titers from various studies. Bell *et al.* reported Hib antibody titer for three doses of its DTaP/PRP-T vaccine:

Hib titer information	2 months pre-immunization	5 months (1 month post-administration)	13 months (9 months post-administration)
GMT (µg/mL) 95% CI	0.27 (0.24-0.31)	0.48 (0.41-0.57)	0.25 (0.22-0.29)

The present specification reports the results at 5 months after administration, *i.e.*, one month after the administration of 3 doses of the claimed composition:

Hib titer information	5 months
GMT (µg/mL) 95% CI	1.46 (1.1-1.9)

While Bell *et al.* notes that other studies of combined DTaP/PRP-T vaccines resulted in Hib GMTs of between 1.66 µg/ml and 1.95 µg/ml, it also notes that these investigators and others consistently observed reduced Hib antibody titer when various Hib vaccines have been combined in the same syringe with aP. These differences in antibody titers is significant because, as Bell *et al.* notes, it has been proposed that the threshold mean Hib antibody titer for continued protection following immunization be raised to 1.0 µg/ml. *Id.* at 639. Thus, whether GMT of Hib antibodies is less or greater that 1.0 µg/ml may have clinical significance.

Furthermore, it is of significance that whereas 82% of subjects manifested seroprotection of >0.15 µg/ml Hib antibody after 3 doses of a DTaP/PRP-T vaccine in Bell (*see* Table 1), 92.1% of the subjects administered the presently claimed vaccine manifested the same level of Hib seroprotection, despite receiving a vaccine comprising a greater number of valencies (*see* Table 4). This could not have been anticipated with any reasonable expectation of success.

The foregoing established that the art recognizes the obstacles faced by the ordinary artisan when preparing a multivalent vaccine of DTP and Hib. The art both recognizes that antigenic competition (wherein following administration of several antigens the immune response to one or more of them is suppressed or diminished) is at play in such compositions and, accordingly, the results observed, particular with regard to the immunogenic response to the Hib conjugate, varies widely and cannot be predicted *a priori* with any reasonable degree of certainty. In particular, given the results of such studies as presented by Eskola II and Bell *et al.*, one of ordinary skill in the art could not have anticipated that the compositions of the present claims would induce Hib antibody titers of > 1 μg/ml and that more than 90% of the population vaccinated with manifest a seroprotective level of Hib antibody.

Extensive clinical trials described in the specification demonstrate that the multivalent immunological compositions of the present invention are safe and efficacious for conferring protection against a broad range of pathogens. P. 25, ll. 18-20. As further stated in the specification (p. 25. ll. 22-25), "These results are surprising insofar as mixtures of numerous vaccine components may have been expected to contribute to the well-recognized phenomena of antigenic competition or interference, whereby certain vaccine components that would be capable of conferring seroprotection when introduced individually into an immunocompetent host become less effective when introduced in combination with other antigens." Such results as observed by the applicants for the presently claimed methods and compositions are further evidence of their non-obviousness *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995) ("One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of `unexpected results,' *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.")

In conclusion, because (a) the prior art fails to provide a particularized teaching or suggestion to make the presently claimed methods and compositions comprising each of the recited antigens, (b) the prior art fails to imbue the ordinary artisan with a reasonable expectation of success (*i.e.*, that the multivalent compositions of the claims would not exhibit antigenic competition), (c) the lack of antigenic competition was unexpected, and the Hib antibody titer is greater than one skilled in the art could have predicted with a reasonable degree of certainty, the presently claims cannot be obvious. Accordingly, the Applicants respect-fully request reconsideration and withdrawal of this rejection.

Respectfully submitted,

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